ARC 6874B

PHARMACY BOARD[657]

Notice of Intended Action

Twenty-five interested persons, a governmental subdivision, an agency or association of 25 or more persons may demand an oral presentation hereon as provided in Iowa Code section 17A.4(1)*"b."*

Notice is also given to the public that the Administrative Rules Review Committee may, on its own motion or on written request by any individual or group, review this proposed action under section 17A.8(6) at a regular or special meeting where the public or interested persons may be heard.

Pursuant to the authority of Iowa Code sections 124.301 and 147.76, the Board of Pharmacy hereby gives Notice of Intended Action to amend Chapter 13, "Sterile Compounding Practices," Iowa Administrative Code.

The proposed amendments clarify the purpose and scope of the rules contained within Chapter 13 and add, delete, and modify definitions of terms used throughout the Chapter. Item 3 amends rule 13.11(155A) to specifically address defined conditions and examples of low-risk preparations and adds new subrule 13.11(3) relating to a new subset of low-risk preparations that are further identified as low-risk preparations with 12-hour or less beyond-use date. The new subrule identifies the conditions and criteria that classify a preparation within this category including the required equipment, area, personnel, and environmental processes. Standards for solid-frozen state are amended in subrules 13.11(1), 13.12(1), and 13.13(1) to comply with current industry standard temperatures for this state and conditions defining high-risk preparations are amended for clarity.

Rule 13.14(155A) is amended in Item 7 to clarify the provisions relating to immediate-use preparations, including the identification of circumstances that would qualify a preparation under this category and the detailing of processes relating to the compounding of immediate-use preparations. Requirements regarding the use of single-dose and multiple-dose vials are clarified in rule 13.15(155A).

The preferred placement of a biological safety cabinet or a compounding aseptic isolator containment and control device to be used in the sterile preparation of hazardous drugs is clarified in Item 9, and terms relating to sterilization methods are corrected and further clarified in Item 10.

Amendments proposed in Item 11 are intended to clarify the purpose for media-fill testing by personnel and provide guidance for the development of appropriate testing procedures. Redundant terms are deleted in Item 12, and Item 13 amends the requirements for periodic microbial air sampling to require semiannual sampling regardless of the level of sterile compounding engaged in at the compounding site. Requests for waiver or variance of the discretionary provisions of these rules will be considered pursuant to 657—Chapter 34.

The amendments were approved at the June 3, 2008, regular meeting of the Board of Pharmacy.

Any interested person may present written comments, data, views, and arguments on the proposed amendments not later than 4:30 p.m. on July 22, 2008. Such written materials may be sent to Terry Witkowski, Executive Officer, Board of Pharmacy, 400 S.W. Eighth Street, Suite E, Des Moines, Iowa 50309-4688; or by E-mail to terry.witkowski@iowa.gov.

These amendments are intended to implement Iowa Code sections 124.301, 126.10, 155A.2, 155A.4, 155A.13, 155A.13A, and 155A.28.

The following amendments are proposed.

ITEM 1. Amend rule 657—13.1(124,126,155A), as follows:

657—13.1(124,126,155A) Purpose and scope. These rules establish standards and procedures for the preparation, labeling, and distribution of sterile preparations by licensed pharmacies pursuant to a ~~physician's~~ practitioner's order or prescription; for sterile product quality and characteristics; for personnel training, environmental quality, and equipment standards; and for pharmaceutical care. Sterile compounding differs from nonsterile compounding primarily by requiring the maintenance of sterility when preparations are compounded exclusively with sterile ingredients and components and by

requiring the achievement of sterility when preparations are compounded with nonsterile ingredients and components. The standards and procedures outlined in this chapter apply to pharmacy practice when a preparation:

ITEM 2. Amend rule 657—13.2(124,126,155A) as follows:

657—13.2(124,126,155A) Definitions. For the purposes of this chapter, the following definitions shall apply:

"Anteroom" or *"ante area"* means an ISO Class 8 or superior area where personnel perform hand hygiene and garbing procedures, staging of components, order entry, preparation labeling, and other high-particulate generating activities.

"Aseptic processing" means a method of preparing pharmaceutical and medical products that involves the separate sterilization of the product and of the package, the transfer of the product into the container, and closure of the container under at least ISO Class 5 conditions and using procedures designed to preclude contamination of drugs, packaging, equipment, or supplies by microorganisms during processing.

"Beyond-use date" means the date or time following compounding after which the preparation shall not be stored~~,~~ or transported~~, or administered~~. The beyond-use date is determined from the date or time compounding of the preparation is completed.

"Biological safety cabinet~~, Class II~~" or *"BSC"* means a ventilated cabinet having an open front with inward airflow for personnel protection, downward HEPA-filtered laminar airflow for product protection, and HEPA-filtered exhausted air for environmental protection.

"Buffer area" or *"cleanroom"* means a room or area where the primary engineering control device is physically located and in which the concentration of airborne particles is controlled to meet ~~an ISO Class 7 standard~~ a specified airborne particulate cleanliness class. Microorganisms in the environment are monitored so that a microbial level for air, surface, and personnel gear is not exceeded for a specified cleanliness class. Activities that occur in the buffer area include the preparation and staging of components and supplies used when sterile preparations are compounded.

"Compounding" means the constitution, reconstitution, combination, dilution, or other process causing a change in the form, composition, or strength of any ingredient or of any other attribute of a product.

"Compounding aseptic isolator" or *"CAI"* means a form of barrier isolator specifically designed for compounding pharmaceutical ingredients or preparations. A CAI is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment should not occur unless ~~it~~ the air has first passed through a microbially retentive filter, HEPA minimum.

"Critical site" means a location that includes any component or fluid pathway surfaces or openings, such as vial septa, injection ports, beakers, opened ampoules, and needle hubs, exposed and at risk of direct contact with air, moisture, or touch contamination.

~~*"Critical surface"* means any area that provides an opportunity for exposure to contamination during aseptic processing, including sterilized products, devices, components, and containers used in the preparation, packaging and transferring of compounded sterile preparations.~~

"Hazardous drug" means a pharmaceutical that is antineoplastic, carcinogenic, mutagenic, or teratogenic.

"HEPA" means high efficiency particulate air.

"High-risk preparation" means a sterile preparation that is compounded from nonsterile ingredients; that is compounded with nonsterile components, containers, or equipment and requires terminal sterilization; or that meets the conditions of rule 13.13(155A).

"ISO Class 5" or *"Class 100 condition"* means an atmospheric environment that contains less than 100 particles, 0.5 microns or larger in diameter per cubic foot of air, according to ISO standards.

"ISO Class 7" or *"Class 10,000 condition"* means an atmospheric environment that contains less than 10,000 particles, 0.5 microns or larger in diameter per cubic foot of air, according to ISO standards.

"ISO Class 8" or *"Class 100,000 condition"* means an atmospheric environment that contains less than 100,000 particles, 0.5 microns or larger in diameter per cubic foot of air, according to ISO standards.

"Laminar airflow workbench" or *"LAFW"* means an apparatus designed to provide an ISO Class 5 environment for the preparation of sterile products that uses air circulation in a defined direction that passes through a HEPA filter to remove the initial particles and the particles generated within the controlled environment.

"Low-risk preparation" means a sterile preparation that is compounded with sterile equipment, sterile ingredients, and sterile contact surfaces or that meets the conditions of rule 13.11(155A).

"Media-fill test" or *"MFT"* means a test used to validate aseptic technique of compounding personnel or of processes and to ensure that the processes used are able to produce sterile product without microbial contamination.

~~*"MFT"* means a media-fill test as specified in rule 13.25(155A).~~

"Medium-risk preparation" means a sterile preparation that is compounded with sterile equipment, sterile ingredients, and sterile contact surfaces and involves complex or numerous manipulations of a sterile product or that meets the conditions of rule 13.12(155A).

"Multiple-dose container" means a multiple-unit container for articles or preparations intended for parenteral administration only and usually containing antimicrobial preservatives.

"Negative pressure room" means a room that is at a lower pressure compared to adjacent spaces, creating a net airflow into the room.

"Positive pressure room" means a room that is at a higher pressure compared to adjacent spaces, creating a net airflow out of the room.

"Preparation" or *"compounded sterile preparation"* means a sterile drug or nutrient that is ~~prepared~~ compounded in a licensed pharmacy or other health care-related facility pursuant to the order of a licensed prescriber, which preparation may or may not ~~be~~ contain sterile products.

"Primary engineering control device" means a device or room that provides an ISO Class 5 environment during the compounding process. Such devices include, but may not be limited to, laminar airflow workbenches (LAFWs), biological safety cabinets (BSCs), and compounding aseptic isolators (CAIs).

"Product" means a commercially manufactured sterile drug or nutrient that has been evaluated for safety and efficacy by the FDA.

"Segregated compounding area" means a designated space, either a demarcated area or room, which is restricted to preparing low-risk preparations with 12-hour or less beyond-use date. A segregated compounding area shall contain a device that provides unidirectional airflow of ISO Class 5 air quality for the compounding of sterile preparations and shall be void of activities and materials that are extraneous to sterile compounding.

"Single-dose container" means a single-unit container for articles or preparations intended for parenteral administration only, intended for a single use and labeled as such. Examples include prefilled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when labeled for a single use or single dose.

"Sterile compounding" means the aseptic processing in a clean air environment of any pharmaceutical ~~including, but not limited to, the following~~ preparations that are required to be sterile when they are administered ~~to patients: baths and soaks for live organs and tissues,~~ into patient body cavities, central nervous and vascular systems, eyes, and joints, and when used as baths for live organs and tissues, including by not limited to injections (e.g., colloidal dispersions, emulsions, solutions, and suspensions), aqueous bronchial and nasal inhalations, irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants.

ITEM 3. Amend rule 657—13.11(155A) as follows:

657—13.11(155A) Low-risk preparations and low-risk preparations with 12-hour or less beyond-use date.

13.11(1) *Conditions defined—low-risk preparations.* Preparations compounded under all of the following conditions are at a low risk of contamination.

a. The preparations are compounded with aseptic manipulations entirely within ISO Class 5 or superior air quality using only sterile ingredients, products, components, and devices.

b. The compounding involves only transferring, measuring, and mixing ~~no~~ not more than three commercially manufactured packages of sterile products and not more than two entries into any one container (e.g., bag, vial) of sterile product or administration container or device to make the preparation.

c. Manipulations are limited to aseptically opening ampoules, penetrating sterile stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, containers of other sterile products, and containers for storage and dispensing.

d. In the absence of the preparation's passing a sterility test and provided that the preparation is properly stored before administration, storage periods shall not exceed the following:

(1) At controlled room temperature for 48 hours;

(2) At a cold temperature for 14 days; or

(3) In a solid-frozen state ~~at~~ between minus ~~20~~ 25 and minus 10 degrees Celsius ~~or colder~~ for 45 days.

13.11(2) *Examples—low-risk preparations.* Examples of low-risk compounding include:

a. The single-volume transfer of sterile dosage forms from ampoules, bottles, bags, and vials using sterile syringes with sterile needles, other administration devices, and other sterile containers. When ampoules are employed, solution content shall be passed through a sterile filter to remove any particles.

b. The manual measuring and mixing of no more than three manufactured products including an infusion or diluent solution to compound drug admixtures and nutritional solutions.

13.11(3) *Low-risk preparations with 12–hour or less beyond-use date.* If the primary engineering control device is a CAI and does not meet the requirements described in subrule 13.27(3) or is a BSC or LAFW that cannot be located within an ISO Class 7 buffer area, then only low-risk level nonhazardous and radiopharmaceutical preparations compounded pursuant to a prescriber's order for a specific patient may be prepared, and administration of such preparations shall commence within 12 hours of compounding or as recommended in the manufacturers' package insert, whichever is less. Preparations shall meet all four of the following criteria:

a. The primary engineering control device shall be certified and shall maintain ISO Class 5 for exposure of critical sites and shall be in a segregated compounding area restricted to sterile compounding activities that minimize the risk of preparation contamination.

b. The segregated compounding area shall not be in a location that has unsealed windows or doors that connect to the outdoors or high traffic flow, or that is adjacent to construction sites, warehouses, food preparation areas, or other areas presenting a risk of contamination.

c. Personnel shall be appropriately garbed and shall perform appropriate cleansing activities prior to compounding. Sinks should be separated from the immediate area of the ISO Class 5 primary engineering control device.

d. Appropriate procedures for cleaning and disinfecting the sterile compounding areas, for personnel training and competency evaluation, for aseptic practices and cleaning or disinfecting processes, and for environmental air sampling and testing shall be followed.

ITEM 4. Amend paragraph **13.12(1)"d"** as follows:

d. In the absence of the preparation's passing a sterility test and provided that the preparation is properly stored before administration, storage periods shall not exceed the following:

(1) At controlled room temperature for 30 hours;

(2) At a cold temperature for 9 days; or

(3) In a solid-frozen state ~~at~~ between minus ~~20~~ 25 and minus 10 degrees Celsius ~~or colder~~ for 45 days.

ITEM 5. Amend paragraphs **13.13(1)"c"** and **13.13(1)"e"** as follows:

c. Nonsterile procedures such as weighing and mixing in air quality inferior to ISO Class 7 are performed before sterilization, compounding personnel are not properly garbed and gloved, or nonsterile water-containing preparations are stored for more than six hours.

e. For a sterilized high-risk preparation, in the absence of the preparation's passing a sterility test, the storage periods shall not exceed the following:

(1) At controlled room temperature for 24 hours;

(2) At a cold temperature for 3 days; or

(3) In a solid-frozen state ~~at~~ between minus ~~20~~ 25 and minus 10 degrees Celsius ~~or colder~~ for 45 days.

ITEM 6. Amend rule 657—13.14(155A) as follows:

657—13.14(155A) Immediate-use preparations. ~~For the purpose of~~ The immediate-use provisions of this rule are intended only for those situations where there is a need for emergency or immediate ~~patient care, pharmacies are exempted from requirements described in this chapter for low- and medium-risk preparations~~ administration of a sterile preparation. Such situations may include cardiopulmonary resuscitation, emergency room treatment, preparation of diagnostic agents, or critical therapy where the compounding of the preparation under low-risk level conditions would subject the patient to additional risk due to delays in therapy. Immediate-use preparations are not intended for storage for anticipated needs or for batch compounding. Medium-risk and high-risk preparations shall not be compounded as immediate-use preparations. Immediate-use preparations are exempt from the provisions of rule 13.11(155A) for low-risk preparations only when all of the following criteria are met:

1. ~~Only~~ The compounding process involves simple ~~aseptic measuring and~~ transfer ~~manipulations are performed with~~ of not more than three commercially manufactured packages of sterile ~~commercial drug~~ nonhazardous products ~~including an infusion or diluent solution~~ or diagnostic radiopharmaceutical products from the manufacturers' original containers and not more than two entries into any one container or package of sterile infusion solution or administration container or device. Hazardous drugs shall not be compounded as immediate-use preparations.

2. Unless required for the preparation, the compounding procedure ~~occurs continuously without delays or interruptions and does~~ is a continuous process not to exceed one hour.

3. ~~At no point during preparation are critical surfaces and ingredients of the preparation directly exposed to contact contamination, such as human touch, cosmetic flakes or particulates, blood, human body substances (e.g., nasal and oral excretions and secretions), and nonsterile inanimate sources.~~ During compounding, aseptic technique is followed and, if the preparation is not immediately administered, the preparation is under continuous supervision to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, mix-ups with other sterile preparations, and direct contact with outside surfaces.

4. Administration begins not later than two hours after compounding of the preparation has begun.

5. If administration has not begun within two hours after compounding of the preparation has begun, the preparation is promptly and safely discarded. ~~Immediate-use preparations shall not be stored for later use.~~

6. Unless immediately and completely administered by the person who compounded the preparation or unless immediate and complete administration is witnessed by the person who compounded the preparation, the preparation shall bear a label listing patient identification information, the names and amounts of all ingredients, the name or initials of the person who compounded the preparation, and the exact one-hour beyond-use date and time.

ITEM 7. Amend rule 657—13.15(155A) as follows:

657—13.15(155A) Utilization of single-dose and multiple-dose containers. Pharmacies utilizing single-dose and multiple-dose containers in sterile compounding shall comply with the following:

1. Single-dose containers that are opened or needle-punctured shall be used within one hour if opened in air quality conditions inferior to ISO Class 5. Any remaining contents shall be discarded.

2. Single-dose vials that are continuously exposed to ISO Class 5 or cleaner air shall be used within six hours after initial needle puncture.

3. Opened single-dose ampoules shall not be stored for any period of time under any air quality conditions.

4. Multiple-dose containers with antimicrobial preservatives that are entered or opened shall be used within 28 days of initial entry or opening unless otherwise specified by the manufacturer.

5. Multiple-dose and single-dose sterile products shall not be combined for use as multiple-dose applications.

ITEM 8. Amend paragraph **13.20(3)"a"** as follows:

a. It is preferable for the ISO Class 5 BSC or CAI to be placed in a contained environment, physically separated from other preparation areas, where air pressure is negative and where the ISO Class 5 BSC or CAI is appropriately vented to the outside of the building.

ITEM 9. Amend paragraph **13.24(2)"a,"** as follows:

a. Sterilization by filtration. This method of sterilization involves the passage of a fluid or solution through a sterilizing grade membrane to produce a sterile effluent.

ITEM 10. Amend paragraph **13.24(2)"b,"** as follows:

b. ~~*Thermal*~~ *Terminal sterilization.* Use of saturated steam under pressure, or autoclaving, is the preferred method to terminally sterilize aqueous preparations.

ITEM 11. Amend rule 657—13.25(155A), as follows:

657—13.25(155A) Media-fill testing by personnel. The pharmacy shall develop, maintain, and implement written procedures that include appropriate media-fill testing by personnel authorized to compound preparations. The issues to consider in the development of a media-fill test are media-fill procedures, media selection, fill volume, incubation, time and temperature, inspection of filled units, documentation, interpretation of results, and possible corrective actions required. Tests shall be performed without interruption in an ISO Class 5 environment under conditions that closely simulate the stressful conditions encountered during compounding of the specific risk level preparations for which the test is intended. The pharmacy shall maintain records of media-fill testing performed, and results of testing procedures shall be available to the board or agents of the board. Compounding personnel whose media-fill test vials result in gross microbial colonization shall be immediately reinstructed and reevaluated by expert compounding personnel to ensure correction of all aseptic practice deficiencies.

ITEM 12. Amend subrule 13.27(2) as follows:

13.27(2) *Placement of primary engineering control device.* The primary engineering control device shall be placed in a ~~cleanroom or~~ buffer area where HEPA filters are employed and the air quality is maintained at ISO Class 7. This area shall have cleanable, nonshedding, smooth surfaces; all junctures shall be coved; and all cracks and crevices shall be caulked. The ceiling shall be impervious and hydrophobic. The buffer area shall not contain any drains or sinks. Only the furniture, equipment, supplies and other material required for compounding activities to be performed shall be brought into the room. Such items brought into the room shall be cleaned and disinfected. Placement in buffer areas ~~and cleanrooms~~ of objects and devices not essential to the compounding process is dictated by the measured effect of those objects and devices on the required environmental quality of air atmospheres and surfaces.

ITEM 13. Amend paragraph **13.29(2)"a"** as follows:

a. Air sampling. Microbial sampling of air within the primary engineering control devices, buffer areas, and anterooms is required ~~on a monthly basis for pharmacies engaging in low- and medium-risk compounding and weekly for pharmacies engaging in high-risk compounding~~ at least semiannually as part of the recertification of facilities and equipment. If compounding occurs in multiple locations within an institution, environmental sampling is required for each individual compounding area.